Bristol-Myers Squibb
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November 19, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5600 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D-2445; Draft Guidance, *Clinical Considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA, 64* Federal Resister 47844 (September I, 1999)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA draft guidance.

We commend the U.S. FDA for providing the draft guidance to assist pharmaceutical sponsors in the development of antiretroviral drugs. However, there are several aspects of the draft guidance that appear contrary to the FDA's stated objectives, which we have cited below:

• The primary endpoint for accelerated approval (see page 5 of draft guidance) is recommended to be the percent of subjects with undetectable plasma HIV RNA levels at 24 weeks. In contrast, the use of mean changes in plasma HIV RNA from baseline was considered a useful primary endpoint only in heavily pretreated patient populations. It is the intent of the accelerated approval regulations to permit registration of a drug "based on evidence from adequate and well-controlled studies of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit..." To date, this has been interpreted to be evidence of safety and antiviral activity, which included changes in plasma HIV RNA from baseline. For accelerated approval, we believe this is still an adequate measure of antiviral activity. In contrast, the requirement for a study that would be fully powered to detect differences in the percent of

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subjects with undetectable plasma HIV RNA would mean that the accelerated approval study and traditional approval study would be one and the same, approximately 700 subjects for a two-armed study, followed for 24 and 48 weeks, respectively. This appears to be a substantial increase in the requirements for accelerated approval (increased patient numbers and time for a phase three study) that is not in the spirit or letter of 21 CFR, subpart H.

- The draft guidance (see top of page 3) states that "Collaboration and the use of multiple investigational agents is strongly encouraged; however, phase 3 studies should be designed such that the treatment effect of each drug of interest can be isolated and the potential for drug-drug interactions can be considered." Further elaboration/guidance on how to conduct studies to achieve the desired information would be useful, particularly with regard to the design of studies to determine the treatment effect of two investigational drugs.

- The draft guidance only covers the requirements to obtain approval for New Chemical Entities (NCE's). Discussion or reference to a separate guidance should be added to describe how approval for a new formulation or dosing regimen of an approved product can be obtained.

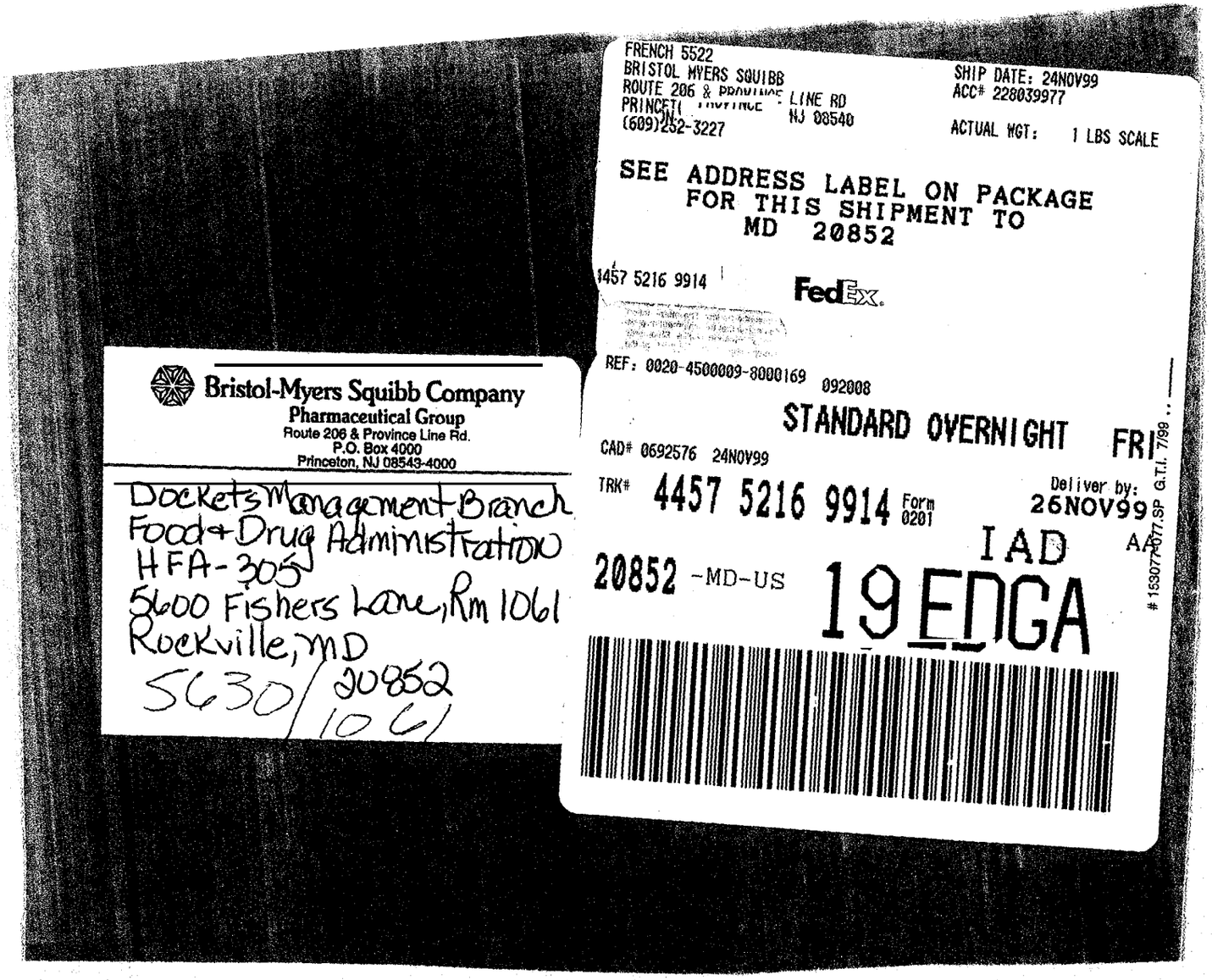
- The guidance does provide information regarding the medical management of patients, which may be inappropriate for the scope and intent of the guidance and FDA's responsibility.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested. Please contact Dr. Echols at (203) 677-6041 if there are any questions.

Sincerely,

Roger M. Echols, M.D.
Vice-President
Infectious Diseases Clinical Research

Laurie F. Smaldone, M.D.
Senior Vice-President
Regulatory Science and Outcomes Research



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